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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	**PAPER NUMBER**
1631	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/817,244	YAKHINI ET AL.	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 May 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56,80-90 and 92-101* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-56,80-90 and 92-101* is/are rejected.

7)☒ Claim(s) *38 and 84* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 4 May 2010 are acknowledged and the amendments are entered.

Claims 1-56, 80-90, and 92-101 are pending and examined in the instant Office action.

Withdrawn Objections

The objections to claims 1, 12-13, 15, and 27 because of informalities are withdrawn in view of amendments filed to the instant set of claims on 4 May 2010.

Claim Objections

The following objections are newly applied:

Claims 38 and 84 are objected to because of the following informalities:

While line 2 of each of claims 38 and 84 recite, "the relevance score is displayed as a ***valued***," this phrase should recite, "the relevance score is displayed as a ***value***."

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

The following rejections are reiterated:

Claims 1-3, 12-13, 15, 20-22, 24, 26-29, and 55-56 are rejected under 35 U.S.C. 102(b) as being anticipated by Cuticchia et al. [CABIOS, 1992, volume 8, pages 467-474].

Claim 1 is drawn to a computer-implemented method for overlaying gene- or protein-related data on chromosome maps to provide at least one data enhanced chromosome map as output. First, the method comprises receiving the chromosome maps to a computer as a first input. Second, the method comprises receiving a list comprising a plurality of gene- or protein- related data items as a second input to a computer, each data item including data other than data specifying a genetic location on said chromosome maps. Third, the method comprises providing an identifier specifying a genetic location for each of the data items on the chromosome map. Fourth, the identifiers are matched with predefined identifiers on the chromosome maps. Fifth, the gene or protein data are re-ordered based on matching the identifiers to an order matching the predefined identifiers on the chromosome maps. Sixth, the biological data items are displayed on the at least one chromosomal map at locations determined by the reordered data items to provide data-enhanced output. All of the steps of this method are automated.

The article of Cuticchia et al. teaches the computer software CMAP, which is a contig mapping and analysis package and relational database for chromosome

construction (see title). The computer apparatus (i.e. automation) and the first step of inputting chromosome maps are taught in the first two paragraphs under “System and methods” on pages 467 to 468 of Cuticchia et al. (automation) and column 1 on page 472 of Cuticchia et al. (first step). The second step of the instant claim is taught in some of the fields in Table I on page 468 of Cuticchia et al. wherein such fields as “Contig Order,” and “Active” are used for importing and teaching the locations of contigs (i.e. pieces of oligonucleotides) within the larger biomolecule or chromosome. The third step of the instant claim is taught in the full paragraph of column 2 on page 468 of Cuticchia et al. wherein additional data identifiers (not locations) such as differences in degrees of hybridizations between clones in the chromosomes are input (i.e. "updated" in the computer). Figure 1 on page 468 of Cuticchia et al. teaches the fourth step of the instant claim wherein the hybridization data is matched within a matrix wherein each cell corresponds to a different location in the library chromosome data (Figure 2B of Cuticchia et al.). The fifth step of the instant claim of reordering the maps is taught in the section “Integration of Physical Maps” in the paragraph bridging columns 1-2 on page 473 of Cuticchia et al. wherein physical and chromosomal maps are merged based on their contents. Figure 1 of Cuticchia et al. also acts as a display (sixth step) for a map of a chromosome that is enhanced with hybridization data.

With regard to claim 2, Figure 1 on page 468 (and the GUI discussed on the same page) of Cuticchia et al. provides and interactive interface for selections of data

types to be displayed (see caption of Figure 1 of Cuticchia et al. which teaches how a user can select specific information from within the matrix).

With regard to claim 3, Figure 1 on page 468 of Cuticchia et al. also illustrates a spatial grouping of biological data of associated genes to a chromosome on a map.

With regard to claim 12, Figure 1 on page 468 of Cuticchia et al. teaches the matching of hybridization data obtained from a distinct source that the chromosome mappings that are displayed.

With regard to claim 13, the data are selected from names of biomolecules published throughout the publication of Cuticchia et al.

With regard to claim 15, the title of Cuticchia et al. teaches use of a relational chromosomal database wherein as in Figure 1 of Cuticchia et al., the tables of hybridization data are cross-referenced with the chromosomal contig data.

With regard to claims 20-22 and 55-56, Figure 1 of Cuticchia et al. compares co-location values of the cells in the matrix to by calculating for each cell, a statistically significant value of *d(a,b)* that assesses hybridization capacity (see full paragraph in column 2 on page 468 of Cuticchia et al. which teaches how differences in hybridization between clones are related to locations and overlap). These values of *d(a,b)* act as

additional hybridization data that are used to annotate the location values of chromosomal data.

With regard to claim 24, the hybridization data of Figure 1 of Cuticchia et al. are interpreted to be relevance scores.

With regard to claim 26, Figure 1 of Cuticchia et al. is interpreted to be scatter plot data.

With regard to claim 27, a plurality of hybridization analyses are used to determine the gene and contig data of Figure 1 of Cuticchia et al.

With regard to claims 28-29, a map of the chromosome along with the degree of hybridization are displayed (i.e. as a heat map) in Figure 1 of Cuticchia et al. This heat map is interpreted to encompass annotations and statistical data.

Response to arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that Cuticchia et al. does not teach the first limitation of chromosomal maps being received as a first input. This argument is not persuasive because column 1 on page 472 of Cuticchia et al. exemplifies adding data into the

CMAP computer software. Among the data input or read into the system in page 472 of Cuticchia et al. are data "fields" corresponding to the locations of each chromosomal clone in the library of chromosomal data (Figure 2B and paragraph bridging columns 1-2 of Cuticchia et al.). The listing of chromosomal clones and their locations is interpreted to be a mapping of the clones- or a chromosome map. It is noted that applicant does not define in the original disclosure the meaning of a chromosomal map (i.e. as an actual image or karyotype). In the absence of such a definition, the Collins English dictionary (2000) provides an accepted meaning of a chromosome map for the purpose of analyzing applicant's arguments as:

> A graphic representation of the positions of genes on chromosomes, obtained by observation of chromosomal bands ***or by determining the degree of linkage between genes***.

As the graphics of Figure 2B and its accompanying text on page 469 of Cuticchia et al. maps the location of a cloned gene to a loci within the chromosomal data, such data input as described in Example 1 on page 472 of Cuticchia et al. encompasses inputting or reading a chromosomal map into the computer system.

Applicant next argues that since Cuticchia et al. allegedly does not teach a chromosome map, the "enhanced" chromosome map (referred to as Figure 1 of Cuticchia et al.) is not a "data-enhanced" chromosome map. This argument is not persuasive because as Figure 2B of Cuticchia et al. maps a location of a cloned gene to chromosomal data, and as Cuticchia et al. takes a matrix of these "already-mapped" clones of genes and adds hybridization assay data to the schematic, Figure 1 is interpreted to be a data-enhanced chromosome map.

Applicant next argues that Cuticchia et al. does not teach identifiers representing genetic locations for each gene on a chromosome map. This argument is not persuasive because Figure 2B of Cuticchia et al. teaches the identifier "L67A12" for a cloned gene. The paragraph bridging columns 1 and 2 on page 469 of Cuticchia et al. teaches that this identifier "L67A12" specifies the location of this clone is row A, column 12 of plate 67 within the Lorist sub-library of chromosomal data.

Applicant next argues that Cuticchia et al. does not teach matching of identifiers to predetermined identifiers on chromosome maps. This argument is not persuasive because Figure 1 of Cuticchia et al. matches identifiers regarding hybridizations to cells in the matrix representing clones of genes; in turn, these genes are mapped by location identifier (as in Figure 2B of Cuticchia et al.) to locations within the chromosomal library.

Applicant next argues that Cuticchia et al. does not reorder the data to an order matching the order of the predetermined identifiers. This argument is not persuasive because since the instant claims do not recite any specific order for the predefined identifiers, the claims are interpreted broadly such that ANY order of the predefined identifiers is the order of the predefined identifiers. As a result, the matching of hybridization data in Figure 1 of Cuticchia et al. is interpreted such that the data items (in this instance, the cells of the matrix) are reordered to match an order of the predefined identifiers.

With regard to claim 3, applicant argues that Cuticchia et al. does not teach spatial groupings of the chromosome maps because Figure 1 of Cuticchia et al. is a representation of a microtitre plate and not a chromosome. This argument is not

persuasive because as discussed above, Figure 1 of Cuticchia et al. encompasses a chromosome map. While applicant argues that Figure 1 of Cuticchia et al. may not be limited to a single chromosome, there is no recitation in the instant claims requiring either the chromosome map or the genes of interest to only be derived from a single chromosome.

With regard to claim 12, applicant argues that Cuticchia et al. does not teach specifying a genetic location for each of the data items be matched with specific information in an accessed external source. This argument is not persuasive, because, Figure 2B specifies the genetic locations for each of the data items. The external source of obtaining and combining data from an additional, external field or source (in this instance, hybridization data) results in Figure 1 of Cuticchia et al.

With regard to claim 13, the gene identifier in Figure 2B, "L67A12," is both published (in the instant CABIOS article) and made up of symbols (in this case, letters and numbers).

With regard to claim 15, a relational database (such as in the title of Cuticchia et al.) is taught in Figure 1 of Cuticchia et al, wherein hybridization data is related to and matched with genetic location data.

With regard to claim 20, applicant argues that the value *d(a,b)* represents a difference in hybridization and does not represent a co-location value. This argument is not persuasive because while the value *d(a,b)* represents a difference in hybridization, the full paragraph in column 2 on page 468 of Cuticchia et al. also states, "The degree to which two clones overlap determines the degree of similarity in their hybridization

profiles. We define *d(a,b)* as the difference in hybridization profiles between clones *a* and *b*." Consequently, the difference in hybridization profile between clones *a* and *b, d(a,b)*, is a co-location value because it is also an indicator of overlap (and thus relative location) between to clones.

With regard to claim 21, applicant argues that the "additional" information is not displayed along a chromosome map. This argument is not persuasive because, as discussed above, Figure 1 of Cuticchia et al. is a chromosome map annotated/enhanced with hybridization data.

With regard to claim 24, applicant argues that relevance scores do not encompass hybridization data. This argument is not persuasive because in the absence of a definition of "relevance scores," the degree of hybridization of a clone is interpreted to be a measure of the relevance of the probe in the system.

With regard to claim 26, applicant argues that Figure 1 of Cuticchia et al. is not a scatter plot or chromosome map. This argument is not persuasive because absent a definition of "scatter plot" in the specification, Figure 1 of Cuticchia et al. (which is interpreted to be a chromosome map for the reasons discussed above) is a scatter plot in that it is a matrix with hybridization data plotted as a function of the abscissa and ordinate axes.

With regard to claim 27, applicant argues that Figure 1 of Cuticchia et al. is a heat map displaying data from plurality of experiments and does not illustrate importing data from a plurality of experiments. This argument is not persuasive because the

combination of Figure 1 of Cuticchia et al. and column 1 on page 472 of Cuticchia et al. teaches both the display and methods of importing data for Figure 1 of Cuticchia et al.

With regard to claim 29, while applicant agrees that Figure 1 of Cuticchia et al. contains data that is annotated, applicant again asserts that Figure 1 is not a chromosome map. For the reasons discussed above, Figure 1 of Cuticchia et al. is a chromosome map.

With regard to claim 55, as explained above with regard to claim 21, applicant argues that the "additional" information is not displayed along a chromosome map. This argument is not persuasive because, as discussed above, Figure 1 of Cuticchia et al. is a chromosome map annotated/enhanced with hybridization data.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following rejections are reiterated:

35 U.S.C. 103 Rejection #1:

Claims 4-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. as applied to claims 1-3, 12-13, 15, 20-22, 24, 26-29, and 55-56 above in further view of Koleszar et al. [US Patent 6,519,583; issued 11 February 2003; filed 27 July 1999].

Claims 4-11 are dependent from claim 1 with the additional features of displaying the genetic data is a specific means wherein each claim identifies a separate feature used to display the data.

Cuticchia et al. teaches the computer-implemented methods for overlaying gene related data on chromosomal maps, as discussed above.

Cuticchia et al. does not explicitly state that every step corresponding to the instant claims with regard to the required display techniques.

The invention of Koleszar et al., entitled, "Graphical viewer for biomolecular sequence data," states in the abstract:

> Disclosed are methods, media and systems for graphically displaying computer-based biomolecular sequence information. Generally, biomolecular sequence information may be graphically depicted in a variety of different forms in accordance with the present invention. The sequence information may be composed of nucleotide or amino acid sequence information or both. The graphical depictions may be in several different formats providing different information relating to the sequences, and may be displayed in one or more screens of a computer user interface.

Figure 4A of Koleszar et al. has the ability to zoom in on regions or zooming out and compressing regions of the genomic sequence of interest as is illustrated on the toolbar of the schematic with pop-up buttons to control the viewing of the features. By zooming into a section of the plot, other sections are cut out of the viewing region (see Figure 4B of Koleszar et al.). Figure 4B of Koleszar et al. also illustrates multiple portions of the chromosome at different magnifications viewed simultaneously. Figure 4B of Koleszar et al. also displays on the same plot both a high (magnified) and mid level view of the plurality of chromosome maps. Additionally, the middle panel of Figure 4B of Koleszar et al. illustrates a detailed view with detailed information on the chromosome map; these high-level, mid-level, and detailed views are interlinked so that the changes in one view changes the other views substantially simultaneously. Tool-tips are displayed at the tops of Figures 4A and 4B and are interpreted to be pop-up dialog boxes.

The purpose of Koleszar et al. in explained in column 2, lines 5-9, which states:

> Accordingly, the development if a display tool which allows a user to clearly and effectively display gene loci information for a given organism or organisms and/or other biomolecular sequences in desirable.

Consequently, Koleszar et al. describes a user friendly, convenient, and effective display of gene loci information.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the chromosomal maps and matrices of Cuticchia et al. by use of the display techniques of Koleszar et al. wherein the motivation would have been that Koleszar et al. has the advantage of displaying the genomic data in a more

convenient and user-friendly format [see, for example, column 2, lines 5-9 of Koleszar et al.].

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of Koleszar et al. does not overcome the alleged deficiencies of Cuticchia et al. This argument is not persuasive because the combination of Cuticchia et al. and Koleszar et al. teaches the required the limitations in the instant set of claims.

Applicant first argues that since Figure 1 of Cuticchia et al. is not a chromosomal map, zooming into a chromosomal map (as is accomplished in Koleszar et al.) is not combinable with Figure 1 of Cuticchia et al. This argument is not persuasive because, as discussed above, Figure 1 of Cuticchia et al. is a chromosomal map. Second, even assuming, *en arguendo*, that Figure 1 of Cuticchia et al. is not chromosome map, the zooming function of Koleszar et al. is generally applicable to any image, including the matrix in Figure 1 of Cuticchia et al.

With regard to claim 6, applicant argues that Figure 4B of Koleszar et al. does not illustrate querying and cutting out data that is not of use. This argument is not persuasive because while the top panel (label 412) illustrates a sequence from 10000 to 30000, the bottom panel expands on only based 15000 to 18000 (cutting out the remaining portions of the sequence). The query for this zooming and cutting out of

unwanted data is shown as a rectangular box within label 412 of Figure 4B of Koleszar et al.

With regard to claim 7, applicant argues that the combination of references does not teach a plurality of chromosome maps. This argument is not persuasive because labels 412, 432, and 452 of Figure 4B of Koleszar et al. comprise a plurality of chromosome map.

With regard to claim 8, applicant argues that whereas claims 8-9 recite the existence of three separate views, Koleszar et al. show at most two separate views. This argument is not persuasive because, as discussed above, Figure 4B of Koleszar et al. illustrates all three views. Specifically, label 412 of Figure 4B of Koleszar et al. teaches a high level view of the chromosome. The high level view is magnified to result in the mid-level view in label 432. This mid-level view is expanded in label 452 of Figure 4B of Koleszar et al. to form the detailed-view which plots detailed information regarding sequence distribution (label 454). With regard to claim 9, modifying the location of the black rectangle in the high view of label 412 of Figure 4B of Koleszar et al. alters the mid-level and detailed views of the chromosome map substantially simultaneously.

With regard to claims 11, applicant argues that Koleszar et al. does not teach pop-up menus. This argument is not persuasive because the buttons on top of the panels in Figures 4A and 4B of Koleszar et al. are interpreted to be pop-up menus. These pop-up menus affect the level of detail of the chromosome map in the high level, middle level and detailed level of Figure 4A and Figure 4B of Koleszar et al.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #2:

Claims 14, 16-19, 23, 25, 30-37, 40-43, 80-83, and 86-89 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. as applied to claims 1-3, 12-13, 15, 20-22, 24, 26-29, and 55-56 above in further view of Schena et al. [PNAS, 1996, volume 93, pages 10614-10619].

Claim 14 is further limiting comprising using official standard gene names.

The article of Cuticchia et al. teaches mappings of data onto chromosomal maps, as discussed above.

While Cuticchia et al. does not demonstrate official standard names, Schena et al. uses accession numbers in Table 1 on page 10616. The article of Schena et al. studies parallel human genome analysis and microarray based expression monitoring of 1000 genes.

Claims 16-17 is further limiting wherein the biomolecule data comprises a plurality of matrices of gene expression data. While Cuticchia et al. teaches matrices of chromosomal data, these matrices do not comprise gene expression data. The article of Schena et al. illustrates matrices of gene expression data in Figure 1 wherein the rows and columns are associated with genes and experiments.

Claims 18-19 are further limiting wherein the rows and columns of the gene expression data are associated with a particular gene and experiment. As explained

above, the article of Schena et al. illustrates matrices of gene expression data in Figure 1 wherein the rows and columns are associated with genes and experiments.

Claim 23 is further limiting wherein the annotations comprise gene ontology. Schena et al. teaches that the ontology of a portion of the genes is from the genus Arabidopsis in the first full paragraph of column 2 on page 10614 of Schena et al.

Claim 25 is further limiting wherein the data is displayed on a single matrix and the additional data is displayed on a second matrix.

While Figure 1 of Cuticchia et al. illustrates a single matrix, Cuticchia et al. does not illustrate a second matrix. Additional matrices with additional information are illustrated in Figure 1 of Cuticchia et al.

Claims 30-33 are further limiting wherein data for the rows of each matrix are calculated, and an auxiliary process is used to obtain cluster data. The results are displayed along side the matrices (i.e. as a heat map with color coding, in a column adjacent to the matrices, or in multiple columns next to the matrices).

Figure 1 of Schena et al. teaches a heat map wherein the colors of the cells within the matrix are interpreted to represent cluster data for each row. The cluster data for each panel for Figure 1 of Schena et al. is subtracted in order to display the resultant cluster data in the for of the matrix in the left panel of Figure 2 of Schena et al. The

colors in the heat map of Figure 2 of Schena et al. are governed by the thresholds in the row underneath the figure.

Claim 34 is further limiting wherein the biomolecular data comprises a microarray of gene expression data, wherein each row is associated with a gene and each column is associated with an experiment. A portion of each matrix is associated with normal tissue and another portion is associated with abnormal tissue.

Cuticchia et al. does not teach gene expression data and resulting matrices.

Figure 1 on page 10615 of Schena et al. illustrates two microarrays of gene expression data; the left matrix of data is normal (-Heat Shock), and the right matrix is abnormal (+Heat Shock). Each row and column of the matrices in Figure 1 of Schena et al. is associated with a gene and an experiment.

With regard to claims 35 and 40, the data in Figure 1 of Schena et al. are displayed in terms of color-coded heat maps.

With regard to claim 36, relevance scores comparing normal (-Heat Shock) to abnormal (+Heat Shock) are displayed as differential expression profiles in Figure 2A of Schena et al.

With regard to claim 37, Cuticchia et al. teaches use of a GUI to display maps in column 2 on page 468.

With regard to claim 41, Cuticchia et al. teaches use of binary codes in Table II in column 1 on page 472.

With regard to claim 42, the shadings in Figure 1 of Cuticchia et al. are interpreted to teach use of density scores, as they are based on locations and hybridization distances *d(a,b)*. The color of the shadings of Figure 1 of Cuticchia et al. demonstrate intervals of density scores (i.e. a grey shaded cell has a density score greater that or equal to a defined density score).

With regard to claim 43, Schena et al. teaches thresholds as the basis for coloring the relevance scores (differential expression profiles of Figure 2 of Schena et al.) in the legend to Figure 2 of Schena et al. This color coding by interval acts to filter data by relevance score (i.e. differential expression value).

Independent claim 80 is drawn to similar subject matter as dependent claim 34, except in independent form. As claim 34 is taught in Cuticchia et al. and Schena et al., independent claim 80 is also taught.

With regard to claim 81, Figure 1 of Schena et al. is interpreted to be a heat map.

With regard to claims 82-83 and 86-87, the relevance scores for Figure 1 of Schena et al. are interpreted to be the differential expression profiles in Figure 2A of Schena et al. Figure 2A of Schena et al. is also interpreted to be a heat map. Furthermore, Cuticchia et al. teaches use of binary codes for similar experiments in Table II in column 1 on page 472.

With regard to claim 88, the shadings in Figure 1 of Cuticchia et al. are interpreted to teach use of density scores, as they are based on locations and hybridization distances *d(a,b)*. The color of the shadings of Figure 1 of Cuticchia et al. demonstrate intervals of density scores (i.e. a grey shaded cell has a density score greater that or equal to a defined density score).

With regard to claim 89, relevance scores comparing normal (-Heat Shock) to abnormal (+Heat Shock) are displayed as differential expression profiles in Figure 2 (left) of Schena et al. The legend beneath Figure 2 teaches the thresholds for displaying the relevant data.

It would have been obvious to one of ordinary skill in the art at the time of the instant invention to modify the chromosomal maps and matrices of Cuticchia et al. by use of the pluralities of gene expression matrices and gene expression differential matrices as in Schena et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, the gene expression profile

matrices of Schena et al. are an alternate form of displaying data related to a gene on a chromosome than the gene hybridization matrix of Cuticchia et al. There would have been a reasonable expectation of success in combining the studies of Schena et al. and Cuticchia et al. because both studies analogously pertain to viewing data regarding chromosomal properties in the form of matrices.

Response to arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of Schena et al. does not overcome the alleged deficiencies of Cuticchia et al. This argument is not persuasive because the combination of Cuticchia et al. and Schena et al. teaches the required the limitations in the instant set of claims.

With regard to claims 21 and 23, applicant argues that Cuticchia et al. does not display the additional information. This argument is not persuasive because, as discussed above, Figure 1 of Cuticchia et al. is a chromosome map annotated/enhanced with hybridization data.

With regard to claim 30, applicant argues that Figures 1 and 2 of Schena et al. do not teach calculation of row vectors that were not calculated. This argument is not persuasive because the two dimensional matrices of Figures 1 and 2 of Schena et al. are comprised of row vectors and column vectors. Furthermore, the row vectors in

Figure 2 of Schena et al. are derived by taking the ratios of the corresponding cells (within the same row vector) with and without heat shock, respectively.

With regard to claims 32 and 33, applicant argues that a matrix with column(s) and with cluster data displayed adjacent to the matrix is not present in Schena et al. This argument is not persuasive because Figures 1 and 2 of Schena et al. are multi-column matrices with the level of gene expression (i.e. cluster data) displayed adjacent to (i.e. on top of) the matrix using a series of colors.

With regard to claim 34, applicant argues that the two arrays in Figure 1 of Schena et al. were not combined to form a single array. Second, applicant argues that Figure 1 may be interpreted to only encompass a single experiment. Third, applicant argues that while Figure 1A of Schena et al. is not conducted on heat shock tissue and Figure 1B of Schena et al. is conducted on heat shock tissue, there is no explicit statement in Schena et al. demonstrating that this study is conducted on normal vs. abnormal tissue. This argument is not persuasive because the caption to Figure 2 of Schena et al. as well as the first paragraph in column 2 on page 10615 of Schena et al. teaches that Figure 2A of Schena et al. is obtained by taking respective ratios of corresponding cells from Figure 1A to Figure 1B of Schena et al. Additionally, in the absence of a definition of "experiment," each cell on each microarray in Figure 1 of Schena et al. is interpreted to encompass an individual experiment. Additionally, in the absence of a definition of normal vs. abnormal tissue, Figure 1A of Schena et al. is interpreted to be conducted on normal tissue in that the tissue is not undergoing heat

shock, and Figure 1B of Schena et al. is interpreted to be conducted on abnormal tissue in that the tissue is undergoing heat shock.

With regard to claim 36, applicant argues that Figure 2A of Schena et al. does not teach relevance scores as separation values. While applicant asserts the alleged meaning of "relevance score" in the Remarks, no definition of this term is present in the disclosure. In the absence of a definition, the differential gene expression in Figure 2A of Schena et al. is interpreted to be encompassed by relevance scores in that the "relevance" of heat shock between normal and heat shocked samples.

With regard to claim 41, applicant argues that the binary codes in Table II of Cuticchia et al. are results of hybridization experimental and are not relevance scores. This argument is not persuasive because, again, absent a limiting definition, the term "relevance scores" is interpreted broadly to encompass results of hybridization experiments.

With regard to claim 42, applicant argues that Figure 1 of Cuticchia et al. represent hybridizations and hybridization distances and not relevance density scores based on distances between genetic locations. This argument is not persuasive because as explained above with regard to claim 20: the value *d(a,b)* represents not only a difference in hybridization, but also degree of overlap of the locations of the clones. As the full paragraph in column 2 on page 468 of Cuticchia et al. states, "The degree to which two clones overlap determines the degree of similarity in their hybridization profiles. We define *d(a,b)* as the difference in hybridization profiles between clones *a* and *b*." Consequently, the difference in hybridization profile between

clones *a* and *b, d(a,b)*, also alludes to distance value because it is also an indicator of overlap (and thus relative location) between to clones. As a result, higher values of *d(a,b)* on the matrix of Figure 1 of Cuticchia et al. signify higher relevance density scores.

With regard to claim 43, applicant argues that Figure 2 of Schena et al. teaches the spread of the data by coloring the data according to known intervals; applicant alleged Schena et al. does not teach filtering of data according to thresholds. This argument is not persuasive because in view of this OBVIOUSNESS rejection, the boundaries of these intervals act as thresholds for differentiating (and filtering) data according to the interval in which the data is located.

With regard to claim 80 (dependent claim 34 is independent form), applicant reiterates the arguments for claim 34. For the reasons discussed above for claim 34, these arguments are not persuasive.

With regard to claim 82 (reciting the subject matter of claim 36, but dependent from claim 80), claim 87 (reciting the subject matter of claim 41, but dependent from claim 82), and claims 88-89 (reciting the subject matter of claims 42-43, but dependent from claim 82), applicant reiterates arguments addressed above for claims 36 and 41-43. For the reasons discussed above, these arguments are not persuasive.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #3:

Claims 38 and 84 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 40-43, 55-56, 80-83, and 86-89 above, and further in view of McCully [US Patent 4,383,994 issued 17 May 1983; filed 19 January 1982].

Claims 38 and 84 are further limiting comprising a "p value."

Cuticchia et al. and Schena et al. make obvious an automated method for mapping genetic information, as discussed above.

Cuticchia et al. and Schena et al. do not use a p-value.

The invention of McCully studies the therapeutic effects of salts as anti-neoplastic agents.

Specifically, example 7 in columns 8-9 of the invention uses a statistical technique to evaluate the effectiveness of the salts in malignancies in mice. Line 60-65 of column 8 of McCully state that the p values can be used to calculate differences between control and experimental samples in mice. This p value acts as a statistical cut off for determining deviation between a control and experimental sample.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the chromosomal ordering maps and matrices of Cuticchia et al. and Schena et al. by use of the statistical criteria of McCully because it is obvious to use a known technique to improve a similar method. In this instance, the use of the statistical criteria of McCully to analyze the arrays of Partridge et al. would have resulted in improved and more advanced statistical analysis. There would have been a reasonable expectation of success in combining these sources because the

statistical techniques of McCully are generally applicable to the analysis of the other references.

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of McCully does not overcome the alleged deficiencies of Cuticchia et al. and Schena et al. This argument is not persuasive because the combination of Cuticchia et al., Schena et al., and McCully teaches the required the limitations in the instant set of claims.

Applicant additionally argues that matrices with expression data are not compared such that results displayed adjacent to the matrix is not present in Schena et al. This argument is not persuasive because Figures 1 and 2 of Schena et al. are multi-column matrices with the level of gene expression displayed adjacent to (i.e. on top of) the matrix using a series of colors.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #4:

Claims 39 and 85 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 40-43, 55-56, 80-83, and 86-89 above, and further in view of Ben-Dor et al. [Genome Research, 2000, volume 10, pages 365-378].

Claims 39 and 85 recite either use of line maps.

Cuticchia et al. and Schena et al. make obvious an automated method or mapping genetic information, as discussed above.

Cuticchia et al. and Schena et al. do not teach line maps.

The article of Ben-Dor et al. studies radiation hybrid ordering.

Specifically, Figure 6 illustrates line maps indicating scores and distances between the relevant markers.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the chromosomal ordering maps and matrices of Cuticchia et al. and Schena et al. by use of chromosomal mapping techniques (i.e. line maps) of Ben-Dor et al. because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the line maps and the densities of Ben-Dor et al. are an alternate means of analyzing the mappings of chromosomes. There would have been a reasonable expectation of combining Cuticchia et al. and Schena et al. with Ben-Dor et al. because they all pertain to analogous subject matter of chromosomal mapping.

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of Ben-Dor et al. does not overcome the alleged deficiencies of Cuticchia et al. and Schena et al. This argument is not

persuasive because the combination of Cuticchia et al., Schena et al., and Ben-Dor et al. teaches the required the limitations in the instant set of claims.

Applicant argues on pages 26-27 of the Remarks that there is no advantage or motivation for choosing line maps as opposed to the numerous other means for mapping chromosomes. This argument is not persuasive because as line maps are an alternate means for mapping the same information using a substitute (are equivalents), it is adequate for an obviousness prior art rejection. There is a reasonable expectation of success in combining Cuticchia et al., Schena et al., and Ben-Dor et al. because all three studies pertain to means for mapping chromosomal data.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #5:

Claims 44-47, 49, 52-54, 90, 92-93, 95, and 98-101 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. as applied to claims 1-3, 12-19, 20-37, 40-43, 55-56, 80-83, and 86-89 above, and further in view of Pollack et al. [Nature Genetics, volume 23, 1999, pages 41-46].

Claims 44 and 90 are further limiting wherein matching chromosomal copy abnormality data with the gene related data identifiers and displaying this data along side the gene-related data.

Claims 46-47 and 92-93 are further limiting wherein the chromosomal copy number information is interlaced and the chromosomal copy number is displayed in color on heat maps.

Claim 49 is further limiting with the additional limitations of having third and fourth matrices each represented by chromosomal abnormality values.

Claim 45 is further limiting wherein one-to-one matching is executed between the cells of the third matrix (chromosomal copy numbers) to the first matrix and from the fourth matrix to the second matrix.

Claim 52 is further limiting wherein the chromosomal copy matrices are in the form of heat maps.`

Claim 101 is an independent claim drawn to similar subject matter as dependent claim 49, except as an independent claim.

Claim 98 is further limiting wherein the matrices are in the form of heat maps.

Claims 53-54 and 99-100 are further limiting with density scores and relevance scores that are based on genetic locations, identifiers, and thresholds.

Cuticchia et al. teaches enhanced mapping of data onto chromosomal maps, as discussed above. The shadings in Figure 1 of Cuticchia et al. are interpreted to teach use of density scores, as they are based on locations and hybridization distances *d(a,b)*. The color of the shadings of Figure 1 of Cuticchia et al. demonstrate intervals of density scores (i.e. a grey shaded cell has a density score greater that or equal to a defined density score). Additionally, Cuticchia et al. provides a means for annotating or "interlacing" the chromosomal map with 1024 bytes of information explaining abnormalities (i.e. chromosomal copy numbers) [see paragraph bridging columns 1-2 on page 471 of Cuticchia et al.]

However, Cuticchia et al. does not teach abnormal copy numbers, or the one-to-one correspondences between the third and fourth matrices and the first and second matrices, respectively.

Schena et al. teaches separate gene expression matrices under abnormal and normal conditions. Specifically, Figure 1 of Schena et al. illustrates two matrices of gene expression under normal [-heat shock] and abnormal [+heat shock] conditions. Schena et al. continue the same analysis with normal [-phorbol ester] and abnormal [+phorbol ester], respectively [data not shown]. However, Figure 2 illustrates a "third" matrix related to heat shock (left) and a "fourth" matrix related phorbol ester (right). Each matrix in Figure 2 of Schena et al. corresponds to a one-to-one ratio between the cells in the original two matrices (i.e. normal vs. abnormal- cell by cell) from which a differential is measured to generate values for each of the cells in Figure 2 of Schena et al. Also, as explained above, the legend of Figure 2 of Schena et al. teaches relevance score and their thresholds used to encode for different range of relevance scores in Figure 2.

However, Schena et al. does not teach that these additional matrices are related to chromosomal copy numbers.

The article of Pollack et al. studies genome-wide analysis of DNA copy-number changes using cDNA microarrays.

Specifically, Figure 5a on page 44 of Pollack et al. illustrates a color coded heat map (red and green) for determining the genetic states of normal vs. diseased breast cancer samples.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the chromosomal mapping techniques of Cuticchia et al. and Schena et al., by use of the color coded heat map plots of Pollack et al. wherein the motivation would have been that the use of such plots allow more conveniently acquired and well resolved data [see lines 13-17 of abstract on page 41 and Figure 5a of Pollack et al.] It would have been further obvious to modify differential gene expression to analyze abnormalities as in Cuticchia et al. and Schena et al. by use of the disease analysis by chromosomal copy number analysis as in Pollack et al. because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, abnormality analysis by chromosomal copy analysis in matrices is an alternate form of abnormality analysis by measuring differential expression analysis. There would have been a reasonable expectation of success in combining Cuticchia et al., Schena et al., and Pollack et al. because all three of the studies analogously rely on comparison of array data to determine genetic abnormalities.

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of Pollack et al. does not overcome the alleged deficiencies of Cuticchia et al. and Schena et al. This argument is not persuasive because the combination of Cuticchia et al., Schena et al., and Pollack et al. teaches the required the limitations in the instant set of claims.

With regard to claim 45, applicant argues that Figure 1 and 2 of Schena et al. do not demonstrate the associations (i.e. between rows and columns of the first and third matrices or the rows and columns of the second and fourth matrices) recited in the instantly rejected claim. This argument is not persuasive because the same microarray preparation is used for each of the four microarrays (see "Microarray Preparation" [singular]) in column 2 on page 10614 of Schena et al. In other words, the same microarray setup is used four times (no Heat shock, Heat Shock, no Phorbol ester, phorbol ester). Thus, each of the four microarray setups corresponds to one of the four matrices wherein the location for each cell (i.e. row, column) within the microarray setup corresponds to the same gene expression analysis in each of the four matrices.

With regard to claims 46 and 92, applicant argues that Cuticchia et al. does not teach the interlacing of chromosomal copy data with the data matrices. This argument is not persuasive because the combination of Cuticchia et al. (which teaches the ability to interlace and annotate chromosomal files with abnormality information- page 471 of Cuticchia et al.) and Pollack et al. (which teaches the annotating matrices with chromosomal abnormality data- Figure 5a) makes this limitation obvious.

With regard to claim 80 (dependent claim 34 is independent form), applicant reiterates the arguments for claim 34. For the reasons discussed above for claim 34, these arguments are not persuasive.

With regard to claims 53-54 (reciting the subject matter of claims 42-43, but dependent from claim 49), applicant reiterates arguments addressed above for claims 42-43. For the reasons discussed above, these arguments are not persuasive.

With regard to claim 101 (similar to dependent claim 45 is independent form), applicant reiterates the arguments for claim 45. For the reasons discussed above for claim 45, these arguments are not persuasive.

With regard to claims 95 and 98-100 (reciting the subject matter of claims 36, 39, and 42-43, but dependent from claim 10), applicant reiterates arguments addressed above for claims 36, 39, and 42-43. For the reasons discussed above, these arguments are not persuasive.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #6:

Claims 50 and 96 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. in view of Pollack et al. as applied to claims 1-3, 12-37, 40-47, 49, 52-56, 80-83, 86-89, 92-93, 95, and 98-101 above, and further in view of McCully [US Patent 4,383,994 issued 17 May 1983; filed 19 January 1982].

Claims 50 and 96 are further limiting comprising a “p value.”

Cuticchia et al., Schena et al., and Pollack et al. make obvious an automated method for mapping genetic information using chromosomal copy data, as discussed above.

Cuticchia et al., Schena et al., and Pollack et al. do not use a p-value.

The invention of McCully studies the therapeutic effects of salts as anti-neoplastic agents.

Specifically, example 7 in columns 8-9 of the invention uses a statistical technique to evaluate the effectiveness of the salts in malignancies in mice. Line 60-65 of column 8 of McCully state that the p values can be used to calculate differences between control and experimental samples in mice. This p value acts as a statistical cut off for determining deviation between a control and experimental sample.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the chromosomal ordering maps and matrices of Cuticchia et al., Schena et al., and Pollack et al. by use of the statistical criteria of McCully because it is obvious to use a known technique to improve a similar method. In this instance, the use of the statistical criteria of McCully to analyze the arrays of Partridge et al. would have resulted in improved and more advanced statistical analysis. There would have been a reasonable expectation of success in combining these sources because the statistical techniques of McCully are generally applicable to the analysis of the other references.

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of McCully does not overcome the alleged deficiencies of Cuticchia et al., Schena et al., and Pollack et al. This argument is not persuasive because the combination of Cuticchia et al., Schena et al., Pollack et al., and McCully teaches the required the limitations in the instant set of claims.

The following rejections are reiterated:

35 U.S.C. 103 Rejection #7:

Claims 48, 51, 94, and 97 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cuticchia et al. in view of Schena et al. in view of Pollack et al. as applied to claims 1-3, 12-37, 40-47, 49, 52-56, 80-83, 86-89, 92-93, 95, and 98-101 above, and further in view of Ben-Dor et al. [Genome Research, 2000, volume 10, pages 365-378].

Claims 48, 51, 94, and 97 recite either use of line maps.

Cuticchia et al., Schena et al., and Pollack et al. make obvious an automated method for mapping genetic information, as discussed above.

Cuticchia et al., Schena et al., and Pollack et al. do not teach line maps.

The article of Ben-Dor et al. studies radiation hybrid ordering.

Specifically, Figure 6 illustrates line maps indicating scores and distances between the relevant markers.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the chromosomal ordering maps and matrices of Cuticchia et al., Schena et al., and Pollack et al. by use of chromosomal mapping techniques (i.e. line maps) of Ben-Dor et al. because it is obvious to substitute known elements in the prior art to yield a predictable result. In this instance, the line maps and the densities of Ben-Dor et al. are an alternate means of analyzing the mappings of chromosomes. There would have been a reasonable expectation of combining

Cuticchia et al., Schena et al., and Pollack et al. with Ben-Dor et al. because they all pertain to analogous subject matter of chromosomal mapping.

Response to Arguments:

Applicant's arguments filed 4 May 2010 have been fully considered but they are not persuasive.

Applicant first argues that the reference of Ben-Dor et al. does not overcome the alleged deficiencies of Cuticchia et al., Schena et al., and Pollack et al. This argument is not persuasive because the combination of Cuticchia et al., Schena et al., Pollack et al., and Ben-Dor et al. teaches the required the limitations in the instant set of claims.

Conclusion

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 8:30 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Russell S. Negin/
Examiner, Art Unit 1631
8 July 2010